DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration Rockville, MD 20857

Dr. Scott A. Masten
Office of Chemical Nomination and Selection
NIEHS/NTP
P.O. Box 12233 MD A3-07
Research Triangle Park, NC 27709

RE: Federal Register Announcement: June 12, 2002 (Vol. 67, No. 113); Request for Public Comments on Substances Nominated to the NTP for Toxicological Studies and on Study Recommendations Made by the NTP Interagency Committee for Chemical Evaluation and Coordination.

Dear Dr. Masten,

The FDA Center for Veterinary Medicine (CVM) supports the toxicological testing of p-toluenesulfonamide (p-TSA) by the NTP. We have read the public comment submitted to you by Edwin C. Bisinger Jr. (representing Akzo Nobel Chemicals, Inc.), dated August 12, 2002, that is posted on the NTP website. We can confirm that Mr. Bissinger's statement that Akzo Nobel has satisfied our data requirements for evaluating the genotoxicity of chloramine-T and it's primary metabolite, p-TSA, is accurate. The difficulty is that Akzo Nobel's data are not available to the public domain for use in human health risk assessments.

In the supporting documentation for chloramine-T and p-TSA available on the NTP website (http://ntp-server.niehs.nih.gov/htdocs/Chem_Background/ExSumPdf/ChloramineT.pdf) and reviewed by the ICCEC, it is stated that U.S. production of p-TSA was between one and ten million pounds in 1998. In addition, the documentation notes that p-TSA is present as a contaminant in saccharin, it is released into the environment during commercial production and can appear in drinking water, it is present in nail polish and in packaging materials that come into direct contact with aqueous and fatty foods. Therefore, it is clear that a high level of public exposure already exists and the level may be increased through the use of chloramine-T in aquaculture. The supporting documentation does not address the fact that chloramine-T rapidly degrades to p-TSA in aqueous environments. Therefore, uses of chloramine-T reported in the supporting documentation such as in wet-to-dry dressings for the treatment of burns, mouth washes, oral irrigation solutions and in whirlpool baths would most likely provide additional human exposure to p-TSA. The ability to assess the risk to public health resulting from these various sources and levels of exposure to p-TSA is severely hindered by the limited toxicity data available. Therefore, we believe that generation of data on the toxicity of p-TSA by the NTP for public use is justified and should be supported.

Because p-TSA is the compound of primary human food safety interest to us, we recommend that the NTP conduct toxicity studies on p-TSA that are consistent with studies we utilize to evaluate the human food safety of drug residues that may occur in the edible tissues of animals. Having

such information in the public domain would be supportive of CVM's mission. Other interested parties may have different recommendations based on different uses, routes and levels of human exposure to chloramine-T or p-TSA. While we would prefer studies performed with p-TSA, studies with chloramine-T would also be acceptable to CVM. We would encourage others to provide their recommendations to you as well. Our specific study recommendations are as follows:

GENOTOXICITY

The FDA/CVM recommends that p-TSA be tested utilizing the current battery of studies recommended by the International Conferences on Harmonization for the testing requirements for veterinary and human drugs (ICH and VICH). This battery includes the following studies:

- Gene Mutation in Bacteria
    - Ames test with *Salmonella typhimurium* strains TA 1535, TA 1537 (or TA97 or TA97a), TA98 and TA 100 and *E. coli* strains WP2 (pKM101), WP2uvrA (pKM101) or *S. typhimurium* TA102.
    - Protocol: OECD Test Guidance 471

- In vitro test for chromosomal effects in mammalian cells
    - Mouse lymphoma test
    - Protocol: OECD Test Guidance 476

- In vivo test for chromosomal effects in rodent hematopoetic cells
    - Micronucleus test
    - Protocol: OECD Test Guidance 474

If p-TSA is determined by the NTP to be mutagenic on the basis of results from these studies, we would recommend that carcinogenicity bioassays in the rat and the mouse be conducted to complete the assessment of the carcinogenic potential of p-TSA. However, CVM would not generally recommend that carcinogenicity studies be conducted for a new animal drug that has a negative genotoxicity battery an no other indicators of carcinogenic potential.

SUBCHRONIC TOXICITY

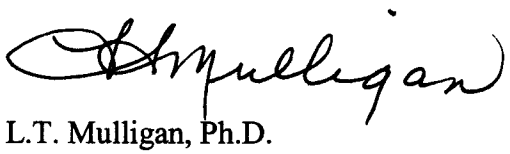
Public information on the subchronic toxicity of p-TSA is also very limited, therefore, we recommend 90-day oral toxicity studies in the rat and the mouse. A published summary report is available for a 90-day study in Wistar rats provided diets containing 100, 300, 1,000 and 3,000 ppm chloramine-T (http://www.emea.eu.int/pdfs/vet/mrls/057099en.pdf). We would propose that a 90-day study conducted by NTP consider these dosages, keeping in mind that the date of the study is uncertain and may or may not have been conducted in compliance with GLP regulations. CVM has no suggestion for the dosing levels for the mouse study. While CVM normally recommends 20 animals per sex per group, the standard NTP protocol utilizing 10 animals per sex per dose level would be suitable for this purpose.

REPRODUCTIVE TOXICITY/TERATOGENICITY

Finally, publicly available information on the teratogenic potential of p-TSA and potential toxicity to the reproductive system is only available in summary form (http://www.emea.eu.int/pdfs/vet/mrls/057099en.pdf) and, therefore, the integrity of the results cannot be evaluated. For this we would recommend a two-generation reproductive toxicity study in the rat and a separate developmental study in the rat. Unfortunately, the only guidance for dose selection for these studies is from the published summary reports. The protocol for the reproductive study is located in OECD Test Guidance 416 and the protocol for the developmental study is located in OECD Test Guidance 414.

We appreciate the opportunity to provide these comments and our support for toxicological testing of p-TSA by the NTP. We will be happy to discuss our recommendations with you further, at your request.

Sincerely,



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